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(71) Applicant *(for all designated States except US)*: **WARNER-LAMBERT COMPANY LLC** [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CONNOLLY, Mike** [US/US]; PFIZER GLOBAL RESEARCH AND DEVELOPMENT, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). **GOGLIOTTI, Rocco, Dean** [US/US]; PFIZER GLOBAL RESEARCH AND DEVELOPMENT, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). **LEE, Helen, Tsenwhei** [US/US]; PFIZER GLOBAL RESEARCH AND DEVELOPMENT, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). **PLUMMER, Mark, Stephen** [US/US]; PFIZER GLOBAL RESEARCH AND DEVELOPMENT, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). **SEXTON, Karen, Elaine** [US/US]; PFIZER GLOBAL RESEARCH AND DEVELOPMENT, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). **VISNICK, Melean** [US/US]; PFIZER GLOBAL RESEARCH AND DEVELOPMENT, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US).

(74) Agents: **FULLER, Grover, F., Jr.** et al.; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).

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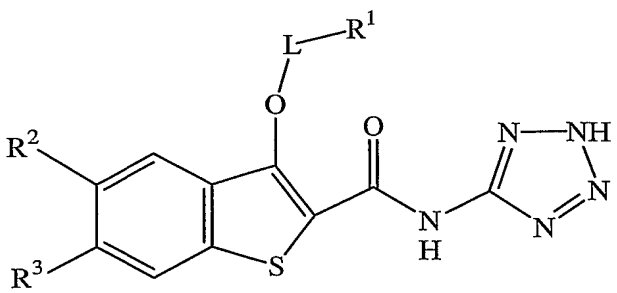
(54) Title: CYCLOALKYL AND HETEROCYCLOALKYL SUBSTITUTED BENZOTHIOPHENES AS THERAPEUTIC AGENTS



(I)

(57) Abstract: The present invention provides benzo[b]thiophenes of Formula (I) wherein R^1, R^2, R^3, and L have any of the values defined therefor in the specification, and pharmaceutically acceptable salts thereof, that are useful as agents in the treatment of diseases and conditions, including inflammatory diseases, cardiovascular diseases, and cancers. Also provided are pharmaceutical compositions comprising one or more compounds of Formula I.

CYCLOALKYL AND HETEROCYCLOALKYL SUBSTITUTED BENZOTHIOPHENES AS THERAPEUTIC AGENTS

CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent application Serial No. 60/476,073 filed on June 5, 2003 the teachings of which are herein incorporated by reference.

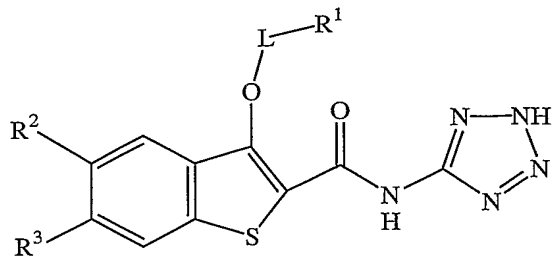
BACKGROUND OF THE INVENTION

Phosphoinositide-3-kinases (PI3Ks) are a family of lipid kinases that phosphorylate phosphoinositols on the 3′-OH to generate PI-3-P (phosphatidylinositol 3-phosphate), PI-3,4-P2 and PI-3,4,5-P3. One class of PI3Ks that are stimulated by growth factors include PI3Kα, PI3Kβ, and PI3Kδ. A separate class of PI3Ks that are activated by G-protein coupled receptors and include PI3Kγ. The growth-factor stimulated PI3Ks (e.g., PI3Kα), have been implicated in cellular proliferation and cancer. PI3Kγ has been demonstrated to be involved in signaling cascades. For example, PI3Kγ is activated in response to ligands such as C5a, fMLP, ADP, and IL-8. In addition, PI3Kγ has been implicated in immune diseases (Hirsch et al. *Science* 2000;287:1049-1053). PI3Kγ null macrophages show a reduced chemotactic response and a reduced ability to fight inflammation (Hirsch et al., 2000, supra). Furthermore, PI3Kγ has also been implicated in thrombolytic diseases (e.g., thromboembolism, ischemic diseases, heart attacks, and stroke) (Hirsch et al. *FASEB J.* 2000;15(11):2019-2021; and Hirsch et al. *FASEB J.*, July 9 2001;10.1096/fj.00-0810fje (cited herein as Hirsch et al., 2001).

Inhibitors of members of the PI3Ks are being developed for the treatment of human disease (see e.g., WO 01/81346; WO 01/53266; and WO 01/83456). There is a need for additional compounds that can inhibit PI3Ks for use as pharmaceutical agents.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides for benzo[b]thiophenes of formula I:



I

or a pharmaceutically acceptable salt thereof;

wherein R^2 and R^3 are selected from the group consisting of:

(i) R^2 is methoxy and R^3 is methyl or methoxy; and

(ii) R^2 is methyl and R^3 is methoxy;

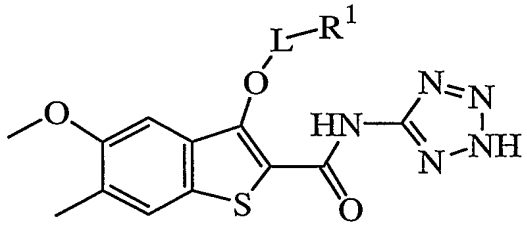
wherein L is absent, or a C_1-C_4-alkylene;

wherein R^1 is C_3-C_8 cycloalkyl, a C_5-C_8 cycloalkenyl, a 4- to 6-membered heterocycloalkyl, a tetrahydropyranyl, a piperidinyl, a oxetanyl, a tetrahydrofuranyl, a bicyclo[2.2.1]heptyl, or decahydro-naphthalenyl,

wherein R^1 can be optionally substituted with 4 methyls, a C_1-C_2 alkylene-6-membered heterocycloalkyl, or from 1 to 3 substitutents independently selected from the group consisting of:

C_1-C_4 alkyl, methyl, tert-butyl, $C(O)CH_3$, $C(O)O$-C_1-C_4alkyl, CH_2-phenyl, a C_5-C_6 cycloalkyl, Cl, Br, F, $-CF_3$, -OH, $-OCF_3$, and O-C_1-C_6alkyl.

In certain embodiments of Formula I, R^2 is methoxy, and R^3 is methyl —a compound of Formula II:



II.

In certain embodiments of Formula II, R^1 is an optionally substituted group selected from the group consisting of: tetrahydropyranyl, C_6-cycloalkyl, C_7-cycloalkyl, and piperidinyl. Examples of compounds of Formula II include, but are not limited to:

5-Methoxy-6-methyl-3-(tetrahydro-pyran-4-yloxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

5-Methoxy-6-methyl-3-(3,3,5,5-tetramethyl-cyclohexyloxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

5-Methoxy-6-methyl-3-(3,3,5-trimethyl-cyclohexyloxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

3-(3,3-Dimethyl-cyclohexyloxy)-5-methoxy-6-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

3-Cyclohexyloxy-5-methoxy-6-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

5-Methoxy-6-methyl-3-(3-methyl-cyclohexyloxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

3-Cycloheptyloxy-5-methoxy-6-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

3-[5-methoxy-6-methyl-2-(2Htetrazol-5-ylcarbamoyl)-benzo[b]thiophen-3-yloxy-piperdine-1-carboxylic acid tert-butyl ester;

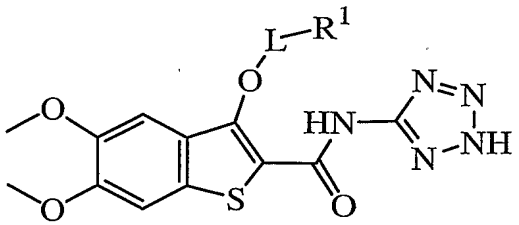
3-(3-Cyclohexyl-propoxy)-5-Methoxy-6-methyl-benzo[b}thiophene-2-carboxylic acid (2H-tetrazol-5-yl) amide;

3-(1-Acetyl-piperidin-4-yloxy)-5-methoxy-6-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

4-[5-Methoxy-6-methyl-2-(2H-tetrazol-5-ylcarbamoyl)-benzo[b]thiophene-3-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; and

5-Methoxy-6-methyl-3-(1-methyl-cyclopropylmethoxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.

In certain embodiments of Formula I, R^2 is methoxy and R^3 is methoxy — a compound of Formula III:



III.

In certain embodiments of Formula III, R^1 is is an optionally substituted group selected from the group consisting of: C_3-cycloalkyl, C_6-cycloalkyl, C_6-cycloalkenyl, and bicyclo[2.2.1]heptyl. Examples of compounds of Formula II include, but are not limited to:

3-(2,2-Dichloro-cyclopropylmethoxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

3-Cyclohexyloxy-5,6-dimethoxy -benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

3-(4-tert-Butyl-cyclohexyloxy)-5,6-dimethoxy -benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

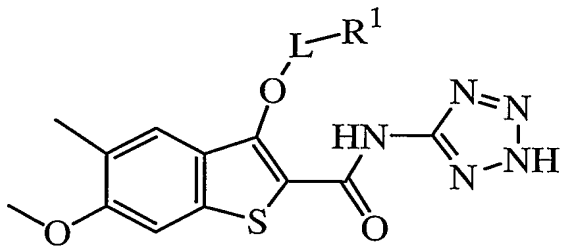
5,6 Dimethoxy-3-(3-methyl-bicyclo[2.2.1]hept-2-ylmethoxy)-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide;

3-(Cyclohex-3-enylmethoxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide;

3-(3,5-Dimethyl-cyclohexloxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide; and

3-(3-Cyclohexyl-propoxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.

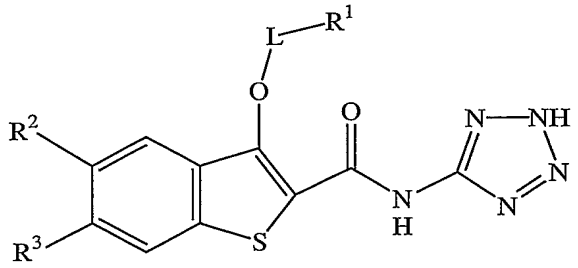
In certain embodiments of Formula I, R^2 is methyl and R^3 is methoxy —a compound of Formula IV:



IV.

In certain embodiments of Formula IV, R^1 is is an optionally substituted C_6-cycloalkyl. An example of a compound of Formula IV is 3-Cyclohexyloxy-6-methoxy-5-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.

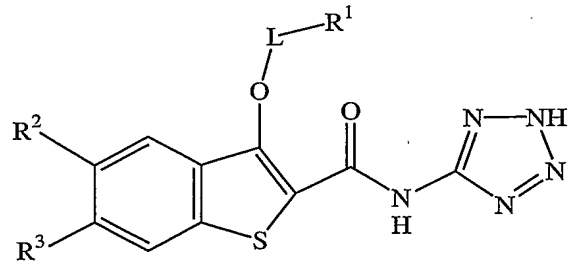
In certain embodiments of Formula I, R^1 is an optionally substituted C_3-C_8 cycloalkyl, cyclohexyl, cyclopentyl, or C_5-C_8 cycloalkenyl —a compound of Formula V:



V.

In certain embodiments of Formula V, L is absent. In other embodiment of Formula V, L is a C_1-C_4-alkylene. An example of a compound of Formula V is 5,6-Dimethoxy-3-(3,3,5-trimethyl-cyclohexyloxy)-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.

In certain embodiments, R^1 is an optionally substituted 4- to 6-membered heterocycloalkyl, a tetrahydropyranyl, a piperidinyl, a oxetanyl, a tetrahydrofuranyl, a bicyclo[2.2.1]heptyl, or decahydro-naphthalenyl—a compound of Formula VI:



VI.

In certain embodiments of Formula VI, L is absent. In other embodiment of Formula VI, L is a C_1-C_4-alkylene. An example of a compound of Formula VI is 5,6-Dimethoxy-3-(tetrahydro-pyran-4-yloxy)-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.

In another aspect, the invention provides for pharmaceutical compositions that comprise a therapeutically effective amount of a compound of Formulas I-VI

and a pharmaceutically acceptable carrier. In certain embodiments, these compositions are useful in the treatment of a PI3K-mediated disorder or condition. The compounds of the invention can also be combined in a pharmaceutical composition that also comprise compounds that are useful for the treatment of cancer, a thrombolytic disease, heart disease, stroke, an inflammatory disease such as rheumatoid arthritis, or another PI3K-mediated disorder.

In another aspect, the present invention provides for methods of treating a subject suffering from a PI3K-mediated disorder or condition comprising: administering, to a subject suffering from a PI3K-mediated condition or disorder, a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formulas I-VI and a pharmaceutically acceptable carrier. In certain embodiments, the PI3K-mediated condition or disorder is selected from the group consisting of: rheumatoid arthritis, osteoarthritis, psoriatic arthritis, psoriasis, inflammatory diseases, and autoimmune diseases. In other embodiments, the PI3K-mediated condition or disorder is selected from the group consisting of: cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease. In still other embodiments, the PI3K-mediated condition or disorder is selected from the group consisting of: cancer, colon cancer, glioblastoma, endometrial carcinoma, hepatocellular cancer, lung cancer, melanoma, renal cell carcinoma, thyroid carcinoma, cell lymphoma, lymphoproliferative disorders, small cell lung cancer, squamous cell lung carcinoma, glioma, breast cancer, prostate cancer, ovarian cancer, cervical cancer, and leukemia. In yet another embodiment, the PI3K-mediated condition or disorder is selected from the group consisting of: type II diabetes. In still other embodiments, the PI3K-mediated condition or disorder is selected from the group consisting of: respiratory diseases, bronchitis, asthma, and chronic obstructive, pulmonary disease. In certain embodiments, the subject is a human.

DEFINITIONS

As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

A "PI3K-mediated disorder or condition" is characterized by the participation of one or more PI3Ks or a PI3P phosphatase, (e.g., PTEN, etc.) in the inception, manifestation of one or more symptoms or disease markers, severity, or progression of a disorder or condition. PI3K-mediated disorders and conditions include, but are not limited to: rheumatoid arthritis, osteoarthritis, psoriatic arthritis, psoriasis, inflammatory diseases, pulmonary fibrosis, autoimmune diseases, cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, coronary artery disease, cancer, breast cancer, gliobastoma, endometrial carcinoma, hepatocellular carcinoma, colon cancer, lung cancer, melanoma, renal cell carcinoma, thyroid carcinoma, small cell lung cancer, squamous cell lung carcinoma, glioma, prostate cancer, ovarian cancer, cervical cancer, leukemia, cell lymphoma, lymphoproliferative disorders, type II diabetes, respiratory diseases, bronchitis, asthma, and chronic obstructive pulmonary disease.

A PI3K is an enzyme that is able to phosphorylate the 3′-OH of a phosphoinositol to generate PI3P. PI3Ks include, but are not limited to, PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ. A PI3K typically comprises at least one catalytic subunit (e.g., p110γ), and may further comprise a regulatory subunit (e.g., p101, etc.).

The term "alkyl group" or "alkyl" includes straight and branched carbon chain radicals. The term "alkylene" refers to a diradical of an unsubstituted or substituted alkane. For example, a "C_{1-6} alkyl" is an alkyl group having from 1 to 6 carbon atoms. Examples of straight-chain alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, etc. Examples of branched-chain alkyl groups include, but are not limited to, isopropyl, *tert*-butyl, isobutyl, etc. Examples of alkylene groups include, but are not limited to, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH(CH_3)-CH_2-$, and $-(CH_2)_{1-6}$. Alkylene groups can be substituted with groups as set forth below for alkyl.

Moreover, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons (e.g., replacing a hydrogen on 1, 2, 3, 4, 5, or 6 carbons) of the hydrocarbon backbone. Such substituents can include, but are not limited to, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo, I, Br, Cl, F, -OH, -COOH, sulfhydryl, (C_1-C_6-alkyl)S-, C_1-C_6-alkylsulfinyl, nitro, cyano, trifluoromethyl, $-NH_2$, =O, =S, =N-CN, =N-OH, $-OCH_2F$, $-OCHF_2$, $-OCF_3$,-SCF_3, $-SO_2-NH_2$, C_1-C_6-alkoxy, -C(O)O-(C_1-C_6 alkyl), -O-C(O)-(C_1-C_6 alkyl), $-C(O)-NH_2$, -C(O)-N(H)-C_1-C_6 alkyl, -C(O)-N(C_1-C_6 alkyl)$_2$, $-OC(O)-NH_2$, -C(O)-H, -C(O)-(C_1-C_6 alkyl), -C(S)-(C_1-C_6 alkyl), $-NR^{70}R^{72}$, where R^{70} and R^{72} are each independently selected from H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, and C(O)-C_1-C_6-alkyl.

Typical substituted alkyl groups thus are aminomethyl, 2-nitroethyl, 4-cyanobutyl, 2,3-dichloropentyl, and 3-hydroxy-5-carboxyhexyl, 2-aminoethyl, pentachloroethyl, trifluoromethyl, 2-diethylaminoethyl, 2-dimethylaminopropyl, ethoxycarbonylmethyl, methanylsulfanylmethyl, methoxymethyl, 3-hydroxypentyl, 2-carboxybutyl, 4-chlorobutyl, and pentafluoroethyl.

"Halo" includes fluoro, chloro, bromo, and iodo.

"Alkenyl" means straight and branched hydrocarbon radicals having 2 or more carbon atoms and comprising at least one carbon-carbon double bond and includes ethenyl, 3-buten-1-yl, 2-ethenylbutyl, 3-hexen-1-yl, and the like. The term "alkenyl" is intended to include both substituted and unsubstituted alkenyl groups. A "C_2-C_6-alkenyl" is an alkenyl group having from from 2 to 6 carbon atoms. Alkenyl groups can be substituted with groups such as those set out above for alkyl. The term "alkenylene" refers to a diradical of a substituted or unsubstituted alkene. Examples of alkenylene groups include, but are not limited to, -CH=CH-, $-CH=CH-CH_2-$, and $-(CH_2)_{1-6}-CH=CH-CH_2-$.

"Alkynyl" means straight and branched hydrocarbon radicals having 2 or more carbon atoms and comprising at least one carbon-carbon triple bond and includes ethynyl, 3-butyn-1-yl, propynyl, 2-butyn-1-yl, 3-pentyn-1-yl, and the like. The term "alkynyl" is intended to include both substituted and unsubstituted

alkynyl groups. Alkynyl groups can be substituted with groups such as those set out above for alkyl. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (e.g., C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term C_2-C_6 includes alkynyl groups containing 2 to 6 carbon atoms. The term "alkynylene" refers to a diradical of a substituted or unsubstituted alkyne. Examples of alkynylene groups include, but are not limited to, -CH≡CH-, -C≡C-CH_2-, and -$(CH_2)_{1-6}$-C≡C-CH_2-.

"Carbocycle" or "Cycloalkyl" means a mono or bicyclic carbocyclic ring functional group including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl, and bicyclo[5.2.0]nonanyl; wherein the cycloalkyl group may optionally contain 1 or 2 double bonds (i.e., a cycloalkylenyl) including, but not limited to, cyclopentenyl, cyclohexenyl, and cycloheptenyl. The term "cycloalkyl" is intended to include both substituted and unsubstituted cycloalkyl groups. Cycloalkyl groups and cyclohexyl groups can be substituted with groups such as those set out above for alkyl. Unless otherwise indicated, the term "(C_3-C_8)cycloalkyl" refers to a cycloalkyl group containing from 3 to 8 carbons. Thus, the term "(C_3-C_8)cycloalkyl" encompasses a monocyclic cycloalkyl group containing from 3 to 8 carbons and a bicyclic cycloalkyl group containing from 6 to 8 carbons. Examples of substituted cycloalkyl groups include, but are not limited to, 2-methyl-cyclohexyl, 3-methyl-cyclohexyl, and 4-methyl-cyclohexyl.

The phrase "4- to 6-membered heterocycloalkyl" means a stable cyclic group having carbon atoms and 1 to 3 heteroatoms independently selected from S, N or O, wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, respectively. Optionally, a 4- to 6-membered heterocycloalkyl may contain 1 or 2 carbon-carbon or carbon-nitrogen double bonds. Illustrative examples of 4- to 6-membered heterocycloalkyl include, but are not limited to, 1-oxa-cyclobutan-2-yl, tetrahydrofuran-3-yl, morpholin-4-yl, 2-thiacyclohex-1-yl, 2-oxo-2-thiacyclohex-1-yl, 2,2-dioxo-2-thiacyclohex-1-yl, and 4-methyl-piperazin-2-yl.

The term "heterocycloalkyl" is intended to include both substituted and unsubstituted heterocycloalkyl groups. Heterocycloalkyl groups can be substituted with 1 to 4 groups such as those set out above for alkyl. Illustrative examples of substituted 3- to 8-membered heterocycloalkyl include 2-hydroxy-aziridin-1-yl, 3-oxo-1-oxacyclobutan-2-yl, 2,2-dimethyl-tetrahydrofuran-3-yl, 3-carboxy-morpholin-4-yl, and 1-cyclopropyl-4-methyl-piperazin-2-yl.

Unless otherwise indicated, the foregoing heterocycloalkyls can be C-attached or N-attached where such is possible and which results in the creation of a stable structure. For example, piperidinyl can be piperidin-1-yl (N-attached) or piperidin-4-yl (C-attached).

Embraced within the term "heterocycloalkyl" are 5 membered rings having one carbon-carbon or one carbon-nitrogen double bond in the ring (e.g., 2-pyrrolinyl, 3-pyrrolinyl, etc.) and 6 membered rings having one carbon-carbon or one carbon-nitrogen double bond in the ring (e.g., dihydro-2H-pyranyl, 1,2,3,4-tetrahydropyridine, 3,4-dihydro-2H-[1,4]oxazine, etc.).

A "4-membered heterocycloalkyl" is a stable 4-membered, monocyclic cycloalkyl ring having 3 carbon atoms and 1 heteroatom selected from the group consisting of: 1 O; 1 S; and 1 N. Illustrative examples of stable 4-membered heterocycloalkyls include oxetanyl, azetidinyl, and thietanyl.

A "5-membered heterocycloalkyl" is a stable 5-membered, monocyclic cycloalkyl ring having from 2 to 4 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of: 1 O; 1 S; 1 N; 2 N; 3 N; 1 S and 1 N; 1 S, and 2 N; 1 O and 1 N; and 1 O and 2 N. Illustrative examples of stable 5-membered heterocycloalkyls include tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, imidazolidinyl, oxazolidinyl, imidazolinyl, isoxazolidinyl, pyrrolidinyl, 2-pyrrolinyl, and 3-pyrrolinyl.

A "6-membered heterocycloalkyl" is a stable 6-membered, monocyclic cycloalkyl ring having from 3 to 5 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of: 1 O; 2 O;1 S; 2 S; 1 N; 2 N; 3 N; 1 S, 1 O, and 1 N; 1 S and 1 N; 1 S and 2 N; 1 S and 1 O; 1 S and 2 O; 1 O and 1 N; and 1 O and 2 N. Illustrative examples of stable 6-membered heterocycloalkyls include tetrahydropyranyl, dihydropyranyl, dioxanyl, 1,3-dioxolanyl, 1,4-dithianyl, hexahydropyrimidine, morpholinyl, piperazinyl, piperidinyl, 2H-

pyranyl, 4H-pyranyl, pyrazolidinyl, pyrazolinyl, 1,2,3,6-tetrahydropyridinyl, tetrahydrothiopyranyl, 1,1-dioxo-hexahydro-1λ^6-thiopyranyl, 1,1-dioxo-1λ^6-thiomorpholinyl, thiomorpholinyl, thioxanyl, and trithianyl.

The term "4- to 6-membered heterocycloalkyl" includes saturated and unsaturated "4- to 6-membered heterocycloalkyls." "4- to 6-membered heterocycloalkyls" may be substituted as set out above for alkyl.

An aryl group is an aromatic hydrocarbon radical. Furthermore, the term "aryl" includes multicyclic aryl groups, for example bicyclic aryl groups such as naphthyl. Typical aryl groups include phenyl, and naphthyl. Phenyl may be unsubstituted or substituted at one or more positions with a substituent such as, but not limited to, those substituents described above for alkyl. Typical substituted phenyl groups include, but are not limited to, 3-chlorophenyl, 2,6-dibromophenyl, 2,4,6-tribromophenyl, 2,6-dichlorophenyl, 4-trifluoromethylphenyl, 3-amino-4-nitrophenyl, 3,5-dihydroxyphenyl, 3-methyl-phenyl, 4-methyl-phenyl, 3,5-dimethyl-phenyl, 3,4,5-trimethoxy-phenyl, 3,5-dimethoxy-phenyl, 3,4-dimethoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 4-tert-butyl-phenyl, 4-hexyl-phenyl, 4-cyano-phenyl, 3,5-di-triflouromethyl-phenyl, 3,5-difluoro-phenyl, 4-chloro-phenyl, 3-trifluoromethyl-phenyl, 4-methoxycarbonyl-phenyl, 2-trifluoromethoxy-phenyl, 3,5-dichloro-phenyl, 2-methoxy-5-methyl-phenyl, 2-fluoro-5-methyl-phenyl, 4-phenoxy-phenyl, 4-chloro-2-trifluoromethyl-phenyl, and the like. Polycyclic aryl groups such as naphthalenyl may be unsubstituted or substituted at one or more positions with a substituent such as, but not limited to, those substituents described above for alkyl. The term "aryl" is intended to include both substituted and unsubstituted phenyl groups.

Some of the compounds in the present invention may exist as stereoisomers, including enantiomers, diastereomers, and geometric isomers. Geometric isomers include compounds of the present invention that have alkenyl groups, which may exist as entgegen or zusammen conformations, in which case all geometric forms thereof, both entgegen and zusammen, *cis* and *trans*, and mixtures thereof, are within the scope of the present invention. Some compounds of the present invention have cycloalkyl groups, which may be substituted at more

than one carbon atom, in which case all geometric forms thereof, both *cis* and *trans*, and mixtures thereof, are within the scope of the present invention. All of these forms, including (R), (S), epimers, diastereomers, cis, trans, syn, anti, (E), (Z), tautomers, and mixtures thereof, are contemplated in the compounds of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

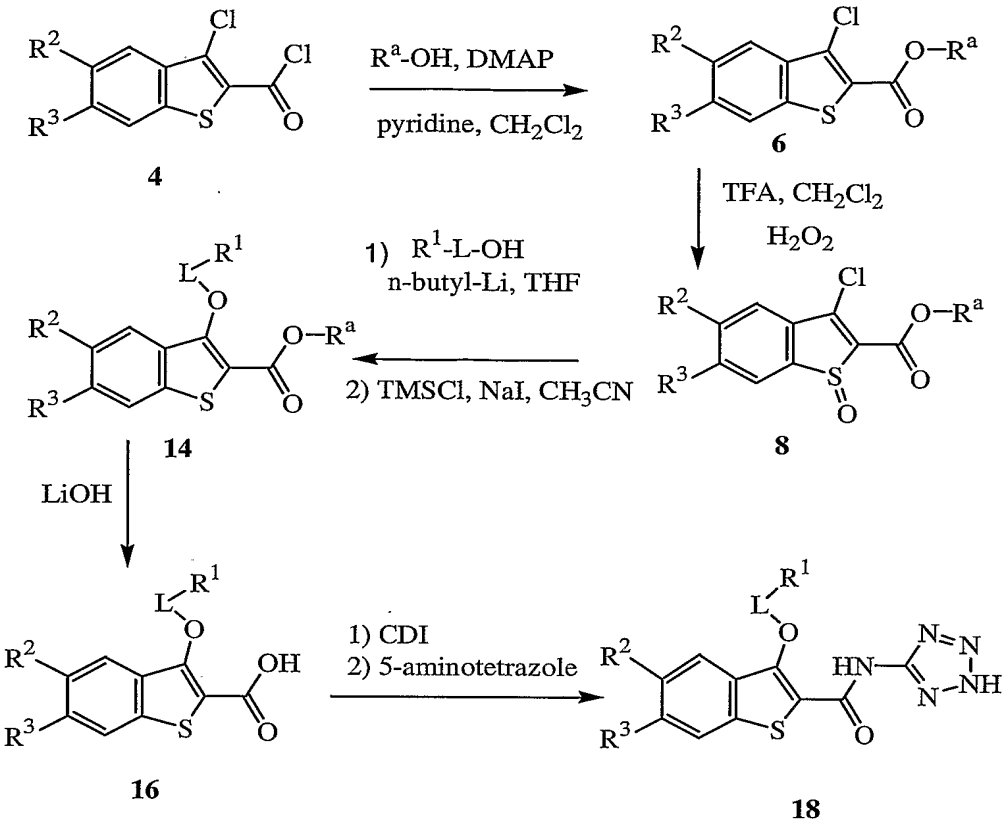
I. INTRODUCTION

The present invention relates to benzo[b]thiophenes of Formulas I-VI, wherein R^1, R^2, R^3, and L have any of the values defined therefor in the specification, and pharmaceutically acceptable salts thereof, that are useful as agents in the treatment of diseases and conditions, including inflammatory diseases, cardiovascular diseases, and cancers. Also provided are pharmaceutical compositions comprising one or more compounds of Formulas I-VI.

II. PREPARATION OF COMPOUNDS

Compounds of the present invention (e.g., compounds of Formulas I-VI) can be prepared by applying synthetic methodology known in the art and synthetic methodology outlined in the schemes set forth below.

Scheme 1



In Scheme 1, an acid chloride **4** (e.g., 3-Chloro-5-methoxy-6-methyl-benzo[b]thiophene-2-carbonyl chloride) is reacted with R^a-OH (e.g., phenol, isopropyl alcohol, methanol, etc.), pyridine or triethylamine (TEA), and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 to yield the ester **6** (e.g., 3-chloro-5-methoxy-6-methyl-benzo[*b*]thiophene-2-carboxylic acid phenyl ester). R^a-OH can be any suitable alcohol, where R^a is a C_1-C_4 alkyl, phenyl, benzyl, isopropyl, methyl, etc., that protects the carboxyl group and can be removed subsequently by base hydrolysis. Acid chlorides of formula **4** can be synthesized using methods that are well-known in the art (see e.g., Pakray and Castle (1986) *J. Heterocyclic Chem.* 23: 1571-1577; Boschelli *et al.* (1995) *J. Med. Chem.* 38: 4597-4614; Connor *et al.* (1992) *J. Med. Chem.* 35: 958-965).

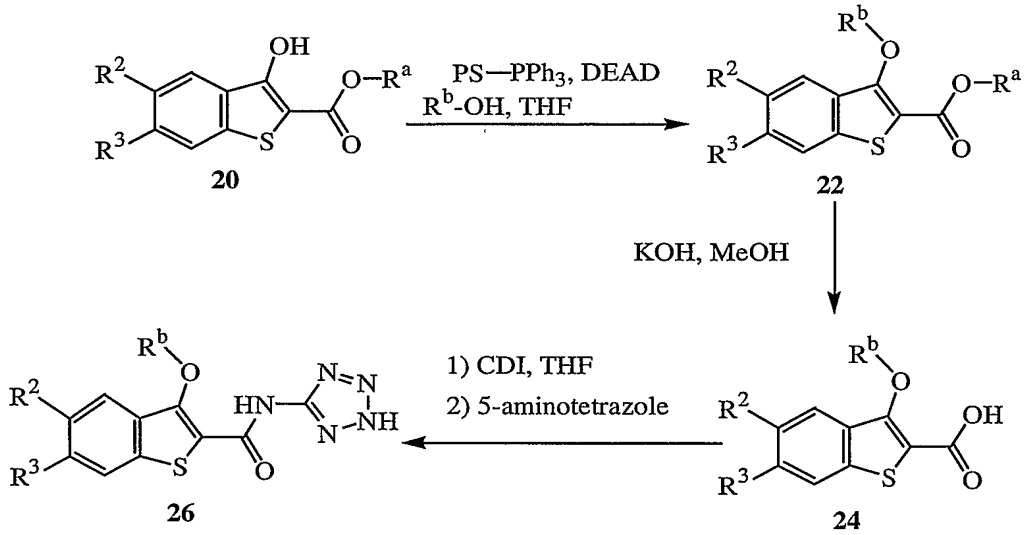
The ester **6** is then oxidized to the 1-oxo-benzo[b]thiophene compound **8** (e.g., 3-chloro-5-methoxy-6-methyl-1-oxo-benzo[b]thiophene-2-carboxylic acid isopropyl ester) using trifluroacetic acid (TFA), CH_2Cl_2, and hydrogen peroxide (H_2O_2). A solution of an alkyl lithium (e.g., n-butyllithium) treated **10** (R^1-L-OH)

in THF is then added to a solution of **8** in THF to yield the 3-substituted benzo[*b*]thiophene **12** (5-methoxy-6-methyl-3-(tetrahydropyran-4-yloxy)-1-oxo-benzo[b]thiophene-2-carboxylic acid isopropyl ester). R^1 and L are as defined herein. A variety of R^1-L-OH compounds can be used including but not limited to, tetrahydro-4H-pyran-4-ol, cyclopentanol, cyclohexyl-methanol, and (3,5-dimethyl-cyclohexyl)-methanol.

12 in acetonitrile is then treated with sodium iodide (NaI) followed by chlorotrimethylsilane (TMSCl) to provide **14** (e.g., 5-methoxy-6-methyl-3-(tetrahydropyran-4-yloxy)-benzo[b]thiophene-2-carboxylic acid isopropyl ester). **14** is then saponified with an inorganic base such as LiOH or NaOH in a solution of MeOH and THF; dioxane and water; or methanol and water, to provide **16** (e.g., 5-methoxy-6-methyl-3-(tetrahydropyran-4-yloxy)-benzo[b]thiophene-2-carboxylic acid). The carboxylic acid **16** is then treated with carbonyl diimidazole (CDI) in a non-protic solvent such as THF (tetrahydrofuran), followed by the addition of a 5-aminotetrazole to provide the carboxamide **18** (e.g., 5-methoxy-6-methyl-3-(tetrahydro-pyran-4-yloxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide).

Alternatively, **16** in anhydrous CH_2Cl_2 can be treated with a catalytic amount of DMF followed by oxalyl chloride. Acetonitrile is then added to this mixture, followed by the addition of 5-aminotetrazole and triethylamine to give **18**.

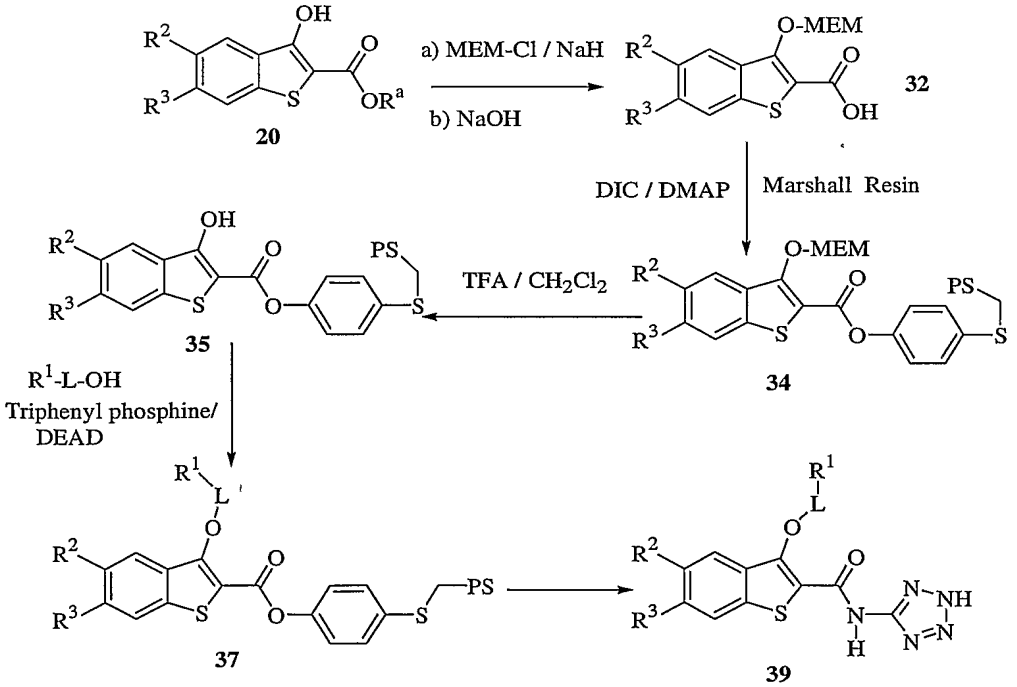
Scheme 2



In Scheme 2, PS-triphenylphosphine (polystyrene-triphenylphosphine) is added to a solution of **20** (e.g., 3-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid methyl ester) in THF under nitrogen gas. Diethyl azodicarboxylate (DEAD) is added, followed by the addition of R^b-OH to yield **22** (e.g., 3-Cyclopropylmethoxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid methyl ester). Compounds such as 3-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid methyl ester can be prepared by the methods describe in U.S. Patent No. 3,954,748. R^b-OH is a compound of formula R^1-L-OH, where L is a C_1-C_4 alkylene or a C_1-C_4-alkylene-C(O)- and R^1 has any one of values defined herein. Examples of R^b-OH include, but are not limited to, 2-cyclopropyl-ethanol, (2,2-dichloro-cyclopropyl)-methanol, cyclohexyl-methanol, and tetrahydro-furan-3-ol.

The ester **22** in methanol is hydrolyzed using an inorganic base, such as potassium hydroxide, to yield the corresponding carboxylic acid **24** (e.g., 3-Cyclopropylmethoxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid). **24** is converted to the carboxamide **26** (e.g., 3-(2-Cyclopropyl-ethoxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide) in an analogous manner to the transformation of **16** to **18** in Scheme 1.

Scheme 3



In Scheme 3, a solid phase synthesis of compound of formula **39** is depicted. A solution of **20** (e.g., 3-hydroxy-5,6-dimethoxy-3-benzo[b]thiophene-2-carboxylic acid methyl ester; Connor *et al.* (1992) *J. Med. Chem.* 35: 958-965) in a solvent such as DMF is treated with a hydride such as potassium hydride or sodium hydride followed by the addition of a suitable hydroxyl protecting group reagent such as MEM-Cl (2-methoxyethoxymethyl chloride; $CH_3OCH_2CH_2OCH_2$-Cl) to give compound **31** (e.g., 5,6-Dimethoxy-3-(2-methoxy-ethoxymethoxy)-benzo[b]thiophene-2-carboxylic acid methyl ester). Those of skill in the art will recognize that other hydroxyl protecting groups in addition to the 2-methoxyethoxymethyl group can be used in Scheme 3 (see e.g., Greene and Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., Chapter 2 (John Wiley & Sons, Inc., 1991)). The ester **31** in THF and water is then hydrolyzed with a base such as NaOH to provide the carboxylic acid **32** (e.g., 5,6-Dimethoxy-3-(2-methoxy-ethoxymethoxy)-benzo[b]thiophene-2-carboxylic acid).

32 in dichloromethane is then conjugated to a solid phase resin such as Marshall resin by reaction with di-isopropyl carbodiimide (DIC) or dicyclohexylcarbodiimide, and Marshall resin (phenol sulfide polystyrene (PS) resin; Marshall and Liener (1970) *J. Org. Chem.* 35: 867-868) to yield **34**. The 2-methoxy-ethoxymethoxy group is then hydrolyzed from **34** in dichloromethane using a suitable acid such as triflouroacetic acid to yield the polymer supported alcohol **35** (e.g., 3-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid-polymer supported).

35 in dichloromethane is combined with a solution of triphenylphosphine and diethylazidodicarboxylate treated R^1-L-OH to yield the R^1-L- substituted compound **37**. **37** is then coupled to 5-amino-tetrazole using triethylamine as described in Scheme 1 to yield **39**.

III. EVALUATION OF COMPOUNDS

Compounds of the present invention (e.g., compounds of Formulas I-VI and pharmaceutically acceptable salts thereof) can be assayed for their ability to inhibit a PI3K. Examples of these assays are set out below and include in vitro and in vivo assays of PI3K activity.

In certain embodiments of the present invention are compounds that selectively inhibit one or more PI3Ks as compared to one or more enzymes including, but not limited to, a cyclic nucleotide dependent protein kinase, PDGF, a tyrosine kinase, a MAP kinase, a MAP kinase kinase, a MEKK, a cyclin-dependent protein kinase. In other embodiments of the invention are compounds that selectively inhibit one PI3K as compared to another PI3K. For example, in certain embodiments, compounds of the present invention display the ability to selectively inhibit PI3Kγ as compared to PI3Kα or PI3Kβ. A compound selectively inhibits a first enzyme as compared to a second enzyme, when the IC_{50} of the compound towards the first enzyme is less than the IC_{50} of the compound towards the second compound. The IC_{50} can be measured, for example, in an in vitro PI3K assay.

In presently preferred embodiments, compounds of the present invention can be assessed for their ability to inhibit PI3Kactivity in an in vitro or an in vivo assay (see below).

PI3K assays are carried out in the presence or absence of a PI3K inhibitory compound, and the amount of enzyme activity is compared for a determination of inhibitory activity of the PI3K inhibitory compound.

Samples that do not contain a PI3K inhibitory compound are assigned a relative PI3K activity value of 100. Inhibition of PI3K activity is achieved when the PI3K activity in the presence of a PI3K inhibitory compound is less than the control sample (i.e., no inhibitory compound). The IC_{50} of a compound is the concentration of compound that exhibits 50% of the control sample activity. In certain embodiments, compounds of the present invention have an IC_{50} of less than about 100 μM. In other embodiments, compounds of the present invention have an IC_{50} of about 1 μM or less. In still other embodiments, compounds of the present invention have an IC_{50} of about 200 nM or less.

PI3Kγ assays have been described in the art (see e.g., Leopoldt et al. *J. Biol. Chem.*, 1998;273:7024-7029). Typically, a sample containing a complex of p101 and p110γ protein are combined with Gβ and Gγ proteins (e.g., G protein β_1/γ_2 subunits). Radiolabeled ATP (e.g., γ-^{32}P-ATP) is then added to this

mixture. The lipid substrates are formed by creating PIP_2 containing lipid micelles. The reactions are then started by adding the lipid and enzyme mixtures and are stopped with the addition of H_3PO_4. The lipid products are then transferred to a glass fiber filter plate, and washed with H_3PO_4 several times. The presence of radioactive lipid product (PIP_3) can be measured using radiometric methods that are well-known in the art.

The activity of growth factor regulated PI3Ks can also be measured using a lipid kinase assay. For example, PI3Kα can be assayed using samples that contain a regulatory and a catalytic subunit. An activating peptide (e.g., pY peptide, SynPep Corp.) is added to the sample with radiolabeled ATP. PIP_2 containing lipid micelles are then added to the sample to start the reaction. The reactions are worked up and analyzed as described for the PI3Kγ assay just described. Assays can also be carried out using cellular extracts (Susa et al. *J. Biol. Chem.*, 1992;267:22951-22956).

IV. PHARMACEUTICALLY ACCEPTABLE SALTS AND SOLVATES

The compounds to be used in the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

The compounds of the present invention (e.g., compounds of Formulas I-VI) are capable of further forming both pharmaceutically acceptable salts, including but not limited to acid addition and/or base salts. Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and base salts (including disalts) thereof. Examples of suitable salts can be found for example in Stahl and Wermuth, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, Wiley-VCH, Weinheim, Germany (2002); and Berge et al., "Pharmaceutical Salts," *J. of Pharmaceutical Science*, 1977;66:1-19.

Pharmaceutically acceptable acid addition salts of the compounds of Formulas I-VI include non-toxic salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorus, and the like, as well as the salts derived from organic acids, such as aliphatic

mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include the acetate, aspartate, benzoate, besylate (benzenesulfonate), bicarbonate/carbonate, bisulfate, caprylate, camsylate (camphor sulfonate), chlorobenzoate, citrate, edisylate (1,2-ethane disulfonate), dihydrogenphosphate, dinitrobenzoate, esylate (ethane sulfonate), fumarate, gluceptate, gluconate, glucuronate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isobutyrate, monohydrogen phosphate, isethionate, D-lactate, L-lactate, malate, maleate, malonate, mandelate, mesylate (methanesulfonate), metaphosphate, methylbenzoate, methylsulfate, 2-napsylate (2-naphthalene sulfonate), nicotinate, nitrate, orotate, oxalate, palmoate, phenylacetate, phosphate, phthalate, propionate, pyrophosphate, pyrosulfate, saccharate, sebacate, stearate, suberate, succinate sulfate, sulfite, D-tartrate, L-tartrate, tosylate (toluene sulfonate), and xinafoate salts, and the like of compounds of Formulas I-VI. Also contemplated are the salts of amino acids such as arginate, gluconate, galacturonate, and the like.

The acid addition salts of the basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metal hydroxides, or of organic amines. Examples of metals used as cations are aluminium, calcium, magnesium, potassium, sodium, and the like. Examples of suitable amines include arginine, choline, chloroprocaine, N,N′-dibenzylethylenediamine, diethylamine, diethanolamine, diolamine, ethylenediamine (ethane-1,2-diamine)glycine, lysine, meglumine, N-methylglucamine, olamine, procaine (benzathine), and tromethamine.

The base addition salts of acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in a conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

V. PHARMACEUTICAL COMPOSITIONS AND METHODS OF ADMINISTRATION

This invention also provides for pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formulas I-VI, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier, diluent, or excipient therefor. The phrase "pharmaceutical composition" refers to a composition suitable for administration in medical or veterinary use. The phrase "therapeutically effective amount" means an amount of a compound, or a pharmaceutically acceptable salt thereof, sufficient to inhibit, halt, or allow an improvement in the disorder or condition being treated when administered alone or in conjunction with another pharmaceutical agent or treatment in a particular subject or subject population. For example in a human or other mammal, a therapeutically effective amount can be determined experimentally in a laboratory or clinical setting, or may be the amount required by the guidelines of the United States Food and Drug Administration, or equivalent foreign agency, for the particular disease and subject being treated.

It should be appreciated that determination of proper dosage forms, dosage amounts, and routes of administration is within the level of ordinary skill in the pharmaceutical and medical arts, and is described below.

A compound of the present invention can be formulated as a pharmaceutical composition in the form of a syrup, an elixir, a suspension, a powder, a granule, a tablet, a capsule, a lozenge, a troche, an aqueous solution, a cream, an ointment, a lotion, a gel, an emulsion, etc. Preferably, a compound of the present invention will cause a decrease in symptoms or a disease indicia

associated with a PI3K-mediated disorder as measured quantitatively or qualitatively.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets contain from 1% to 95% (w/w) of the active compound. In certain embodiments, the active compound ranges from 5% to 70% (w/w). Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1000 mg, preferably 1.0 mg to 100 mg, or from 1% to 95% (w/w) of a unit dose, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions of the present invention (see, e.g., *Remington: The Science and Practice of Pharmacy*, 20th ed., Gennaro et al. Eds., Lippincott Williams and Wilkins, 2000).

A compound of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations (i.e., they can be "nebulized") to be administered via inhalation. Aerosol formulations can be

placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane nitrogen, and the like.

Formulations suitable for parenteral administration, such as, for example, by intravenous, intramuscular, intradermal, and subcutaneous routes, include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and nonaqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. In the practice of this invention, compositions can be administered, for example, by intravenous infusion, orally, topically, intraperitoneally, intravesically or intrathecally. The formulations of compounds can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials. Injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

The dose administered to a subject, in the context of the present invention should be sufficient to affect a beneficial therapeutic response in the subject over time. The term "subject" refers to a member of the class Mammalia. Examples of mammals include, without limitation, humans, primates, chimpanzees, rodents, mice, rats, rabbits, horses, livestock, dogs, cats, sheep, and cows.

The dose will be determined by the efficacy of the particular compound employed and the condition of the subject, as well as the body weight or surface area of the subject to be treated. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular compound in a particular subject. In determining the effective amount of the compound to be administered in the treatment or prophylaxis of the disorder being treated, the physician can evaluate factors such as the circulating plasma levels of the compound, compound toxicities, and/or the progression of the disease, etc. In general, the dose equivalent of a compound is from about 1 μg/kg to 100 mg/kg for a typical subject. Many different administration methods are known to those of skill in the art.

For administration, compounds of the present invention can be administered at a rate determined by factors that can include, but are not limited

to, the LD_{50} of the compound, the pharmacokinetic profile of the compound, contraindicated drugs, and the side-effects of the compound at various concentrations, as applied to the mass and overall health of the subject. Administration can be accomplished via single or divided doses.

Examples of a typical tablet, parenteral, and patch formulation include the following:

TABLET FORMULATION EXAMPLE 1

Tablet Formulation	
Ingredient	Amount
Compound of Formulas I-VI	50 mg
Lactose	80 mg
Cornstarch (for mix)	10 mg
Cornstarch (for paste)	8 mg
Magnesium Stearate (1%)	2 mg
	150 mg

The compounds of the present invention (e.g., a compound of Formulas I-VI, or a pharmaceutically acceptable salt thereof) can be mixed with the lactose and cornstarch (for mix) and blended to uniformity to a powder. The cornstarch (for paste) is suspended in 6 mL of water and heated with stirring to form a paste. The paste is added to the mixed powder, and the mixture is granulated. The wet granules are passed through a No. 8 hard screen and dried at 50°C. The mixture is lubricated with 1% magnesium stearate and compressed into a tablet. The tablets are administered to a patient at the rate of 1 to 4 each day for treatment of a PI3K-mediated disorder or condition.

PARENTERAL SOLUTION FORMULATION EXAMPLE 1

In a solution of 700 mL of propylene glycol and 200 mL of water for injection can be added 20.0 g of a compound of the present invention. The mixture is stirred, and the pH is adjusted to 5.5 with hydrochloric acid. The volume is

adjusted to 1000 mL with water for injection. The solution is sterilized, filled into 5.0 mL ampules, each containing 2.0 mL (40 mg of invention compound), and sealed under nitrogen. The solution is administered by injection to a subject suffering from a PI3K-mediated disorder or condition and in need of treatment.

PATCH FORMULATION EXAMPLE 1

Ten milligrams of a compound of the present invention can be mixed with 1 mL of propylene glycol and 2 mg of acrylic-based polymer adhesive containing a resinous cross-linking agent. The mixture is applied to an impermeable backing (30 cm^2) and applied to the upper back of a patient for sustained release treatment of a PI3K-mediated disorder or condition.

VI. METHODS FOR TREATING PI3K-MEDIATED DISORDERS AND CONDITIONS

The compounds of the present invention and pharmaceutical compositions comprising a compound of the present invention can be administered to a subject suffering from a PI3K-mediated disorder or condition. PI3K-mediated disorders and conditions can be treated prophylactically, acutely, and chronically using compounds of the present invention, depending on the nature of the disorder or condition. Typically, the host or subject in each of these methods is human, although other mammals can also benefit from the administration of a compound of the present invention.

In therapeutic applications, the compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. The term "administering" refers to the method of contacting a compound with a subject. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, parentally, or intraperitoneally. Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally, topically, via implantation, transdermally, topically, and via implantation. In certain embodiments, the compounds of the present

invention are delivered orally. The compounds can also be delivered rectally, bucally, intravaginally, ocularly, andially, or by insufflation.

The compounds utilized in the pharmaceutical method of the invention can be administered at the initial dosage of about 0.001 mg/kg to about 100 mg/kg daily. In certain embodiments, the daily dose range is from about 0.1 mg/kg to about 10 mg/kg. The dosages, however, may be varied depending upon the requirements of the subject, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired. The term "treatment" includes the acute, chronic, or prophylactic diminishment or alleviation of at least one symptom or characteristic associated with or caused by the disorder being treated. For example, treatment can include diminishment of several symptoms of a disorder, inhibition of the pathological progression of a disorder, or complete eradication of a disorder. The compounds of the present invention can be co-administered to a subject. The term "co-administered" means the adminstration of two or more different pharmaceutical agents or treatments (e.g., radiation treatment) that are administered to a subject by combination in the same pharmacetical composition or separate pharamaceutical compositions. Thus co-adminstration involves adminstration at the same time of a single pharmaceutical composition comprising two or more pharmaceutical agents or administration of two or more different compositions to the same subject at the same or different times. For example, a subject that is administered a first dosage that comprises a compound of the present invention at 8 a.m. and then is adminstred CELEBREX® at 1-12 hours later, e.g., 6 p.m., of that same day has been co-administered with a compound of the present invention and CELEBREX®. Alternatively, for example, a subject could be administred with a single dosage comprising a compound of the present invention and CELEBREX ® at 8 a.m. has been co-administered with a compound of the present invention and CELEBREX®.

Thus, compounds of the invention can also be co-administered with compounds that are useful for the treatment of cancer (e.g., cytotoxic drugs such as TAXOL®, taxotere, GLEEVEC® (Imatinib Mesylate), adriamycin, daunomycin, cisplatin, etoposide, a vinca alkaloid, vinblastine, vincristine, methotrexate, or adriamycin, daunomycin, cis-platinum, etoposide, and alkaloids, such as vincristine, farnesyl transferase inhibitors, endostatin and angiostatin, VEGF inhibitors, and antimetabolites such as methotrexate. The compounds of the present invention may also be used in combination with a taxane derivative, a platinum coordination complex, a nucleoside analog, an anthracycline, a topoisomerase inhibitor, or an aromatase inhibitor). Radiation treatments can also be co-administered with a compound of the present invention for the treatment of cancers.

The compounds of the invention can also be co-administered with compounds that are useful for the treatment of a thrombolytic disease, heart disease, stroke, etc., (e.g., aspirin, streptokinase, tissue plasminogen activator, urokinase, anticoagulants, antiplatelet drugs (e.g., PLAVIX®; clopidogrel bisulfate), a statin (e.g., LIPITOR® (Atorvastatin calcium), ZOCOR® (Simvastatin), CRESTOR® (Rosuvastatin), etc.), a Beta blocker (e.g, Atenolol), NORVASC® (amlodipine besylate), and an ACE inhibitor (e.g., Accupril® (Quinapril Hydrochloride), Lisinopril, etc.).

The compounds of the invention can also be co-administered for the treatment of hypertension with compounds such as ACE inhibitors, lipid lowering agents such as statins, LIPITOR® (Atorvastatin calcium), calcium channel blockers such as NORVASC® (amlodipine besylate). The compounds of the present invention may also be used in combination with fibrates, beta-blockers, NEPI inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

For the treatment of inflammatory diseases, including rheumatoid arthritis, the compounds of the invention may be co-administered with agents such as TNF-α inhibitors such as anti-TNFα monoclonal antibodies (such as REMICADE®, CDP-870 and HUMIRA™ (adalimumab) and TNF receptor-immunoglobulin fusion molecules (such as ENBREL®), IL-1 inhibitors, receptor antagonists or

soluble IL-1Rα (e.g. KINERET™ or ICE inhibitors), nonsteroidal anti-inflammatory agents (NSAIDS), piroxicam, diclofenac, naproxen, flurbiprofen, fenoprofen, ketoprofen ibuprofen, fenamates, mefenamic acid, indomethacin, sulindac, apazone, pyrazolones, phenylbutazone, aspirin, COX-2 inhibitors (such as CELEBREX® (celecoxib), VIOXX® (rofecoxib), BEXTRA® (valdecoxib) and etoricoxib, metalloprotease inhibitors (preferably MMP-13 selective inhibitors), NEUROTIN®, pregabalin, low dose methotrexate, leflunomide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The compounds of the invention may be co-administered with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, rofecoxib and etoricoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

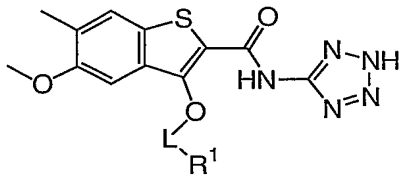
The compounds of the invention may also be co-administered with antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antisepsis compounds such as Valant.

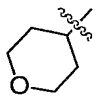
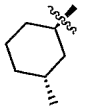
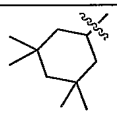
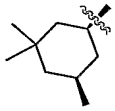
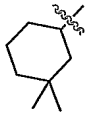
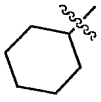
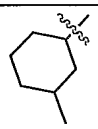
The compounds of the present invention may further be co-administered with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-Dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, NEUROTIN®, pregabalin, COX-2 inhibitors, propentofylline or metryfonate.

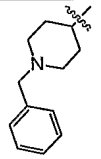
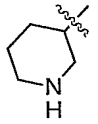
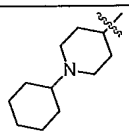
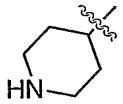
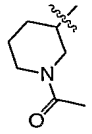
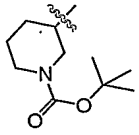
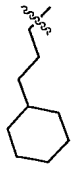
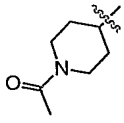
The compounds of the present invention may additionally be co-administered with osteoporosis agents such as EVISTA® (raloxifene hydrochloride) droloxifene, lasofoxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

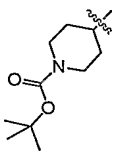
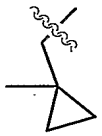
EXAMPLES

Examples 1-18



Ex.	-L-R^1	MS (M+1)	NMR[a]
1		390.1	
2		402.1	
3		444.1	
4		430.1	
5		416.1	
6		388.1	11.09 (s, 1H), 7.77 (s, 1H), 7.22 (s, 1H), 4.56 (sept, 1H), 3.88 (s, 3H), 2.26 (s, 3H), 2.02 (m, b, 2H), 1.72 (m, b, 2H), 1.59 (m, b, 2), 1.47 (m, b, 1H), 1.24 (m, b, 3H)
7		402.1	

Ex.	-L-R^1	MS (M+1)	NMR[a]
8		402.1	
9		479.3	
10		387 (M-1)	9.42 (s,1H), 9.10 (s,1H), 7.80(s,1H), 7.32(s,1H), 4.83(m,1H), 3.95(s,3H), 3.42(m,2H), 3.10(m,2H), 2.30(s,3H), 1.97(m,2H), 1.91(m,1H),1.83(m,1H)
11		469 (M-1)	
12		387 (M-1)	16.16,11.49(s,1H), 8.83(brs,1H),8.58(brs,1H), 7.80(s,1H), 7.22(s,1H), 4.4.76(m,1H), 3.90(s,3H), 3.60-3.40(M,5H), 3.00(m,2H), 2.50(s,3H), 2.18(m,1H), 1.95(m,1H)
13		429 (M-1)	
14		487 (M-1)	7.81(s,1H), 7.25(s,1H), 4.93(brs,1H), 3.91(s,3H), 3.50(brs, 3H), 2.27(s,3H), 2.12-1.90(m,4H), 1.58(brs,1H), 1.13(s,9H).
15		428 (M-1)	7.80(s,1H), 7.28(s,1H), 4.40(t,2H), 3.90(s,3H), 2.27(s,3H), 1.83(m,2H), 1.60(m,4H), 1.35(m,2H), 1.12(M,4H), 0.83(m,2H)
16		429 (M-1)	

Ex.	-L-R^1	MS (M+1)	NMR[a]
17		487 (M-1)	7.79(s,1H), 7.22(s,1H), 4.35(m,1H), (3.86(s,3H), 3.77(m,2H), 2.95(m,2H), 2.23(s,3H), 1.96(m,3H), 1.63(m,2H), 1.33(s,9H).
18		372 (M-1)	16.05(s,1H), 11.04(s,1H), 7.80(s,1H), 7.26(s,1H), 4.25(s,2H), 4.93(s,3H), 2.28(s,3H), 1.26(s,3H), 0.63(m,2H), 0.45(m,2H)

Intermediate 1. **3-methoxy-4-methylcinnamic acid**. 3-(3-methoxy-4-methyl-phenyl)-acrylic acid starting material was prepared according to the following reaction: 3-methoxy-4-methylbenzaldehyde (20.0 mL, 137 mmol) was refluxed with malonic acid (27.2 g, 206 mmol) in a mixture of piperidine (6 mL) and pyridine (200 mL) for 2.5 hours. The mix was concentrated to one half volume. H_2O (~20 mL) and 1N HCl (~6 mL) were added to give a solid precipitate. The solid was filtered and rinsed with 1N HCl and then H_2O and then was dried *en vacuo* to give the title product in quantitative yield. MS: M+1=193.1 (APCI). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 16 Hz, 1H), 7.37 (m, 2H), 6.83 (d, J = 8.8 Hz, 1H), 6.31 (d, J = 15.6 Hz, 1H), 3.87 (s, 3H), 2.23 (s, 3H).

Intermediate 2. **3-Chloro-5-methoxy-6-methyl-benzo[b]thiophene-2-carbonyl chloride.** 3-methoxy-4-methylcinnamic acid (9.18 g, 47.8 mmol)) was dissolved in a mixture of pyridine (0.39 mL), DMF (3.51 mL), and chlorobenzene (60 mL) in an argon purged, round bottom flask fitted with a reflux condenser. Thionyl chloride (17.8 mL, 244 mmol) was added to the mixture via syringe. The reaction was stirred and heated to vigorous reflux for 18 hours. The reaction was allowed to cool to room temperature and then was concentrated *en vacuo*. The residue was dissolved in CH_2Cl_2 (~40 mL) and then was diluted with an excess of hexanes. The dilution was concentrated to about one half volume to give a precipitate. The solid precipitate was filtered, collected, and dried *en vacuo* to give the title product (8.49 g, 32.9 mmol, 69%) as a brown-gray fluffy solid.

Intermediate 3. **3-chloro-5-methoxy-6-methyl-benzo[*b*]thiophene-2-carboxylic acid isopropyl ester.** Intermediate 2 (15.0 g, 54.7 mmol) was stirred with triethylamine (15.2 mL) and catalytic 4-dimethylaminopyridine in isopropanol (70 mL) at 80°C for one hour. The reaction mix was allowed to cool to room temperature and was diluted with water. The dilution was extracted several times with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4, filtered through celite, and concentrated *en vacuo* to give a brown waxy solid that was carried on immediately without further purification.

Intermediate 4. **3-chloro-5-methoxy-6-methyl-1-oxo-benzo[*b*]thiophene-2-carboxylic acid isopropyl ester.** To a 0 °C, stirring solution of Intermediate 3 (16.3 g, 54.7 mmol) in CH_2Cl_2 (55 mL) and Trifluoroacetic acid (55 mL) was added 30% aqueous H_2O_2 (7.43 mL, 65.6 mmol) dropwise via syringe. The reaction was stirred at 0 °C for 15 minutes and then at room temperature for two hours. The mix was chilled again to 0 °C and then added dropwise to a 0 °C saturated aqueous sodium bisulfite solution. The quenched mix was extracted several times with EtOAc. The extracts were washed with brine, dried over Na_2SO_4, and concentrated. The product was purified by silica gel flash chromatography (EtOAc/hexanes (1:4 then 2:3)) to give the title product (16.753 g, 53.4 mmol, 97%) as a solid. MS: M+1 = 315.0 (APCI)

Intermediate 5. **5-methoxy-6-methyl-3-(tetrahydropyran-4-yloxy)-benzo[*b*]thiophene-2-carboxylic acid isopropyl ester.** To a –78 °C solution of tetrahydro-4H-pyran-4-ol (0.167 mL, 1.75 mmol) in anhydrous THF (4.5 mL) was added *n*-butyllithium (1.6 N in hexanes, 1.31 mL, 2.1 mmol). The reaction was stirred at –78 °C for two minutes and then was allowed to warm to room temperature. The solution was added dropwise to a stirring solution of Intermediate 4 (0.500 g, 1.59 mmol) in anhydrous THF (4.5 mL). The reaction was stirred at room temperature for five minutes and then chlorotrimethylsilane (0.563 mL, 4.77 mL) and sodium iodide (0.715 g, 4.77 mmol) were added. The reaction was stirred for ten minutes at room temperature and then was quenched with saturated aqueous sodium thiosulfate. The quenched mixture was diluted with H_2O and was extracted three times with ethyl acetate. The organic extracts

were washed with brine, dried over Na_2SO_4, filtered through celite, and concentrated. The product was purified by silica gel flash chromatography (0 to 20% EtOAc-hexanes gradient elution) to give the title product (0.314 g, 54 % yield) as a solid. MS: M+1=365.3 (APCI).

Intermediate 6. **5-methoxy-6-methyl-3-(tetrahydropyran-4-yloxy)-benzo[*b*]thiophene-2-carboxylic acid**. Intermediate 5 (0.310 g, 0.852 mmol) was stirred with 10% aqueous LiOH (1.6 mL) and dioxane (2.4 mL) at 70°C for one hour. The mix was diluted with saturated aqueous sodium bicarbonate and washed twice with diethyl ether. The aqueous portion was acidified with 1N HCl. The acidified aqueous portion was then extracted several times with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4, filtered through celite, and concentrated to give the title product.

Example 1. **5-Methoxy-6-methyl-3-(tetrahydro-pyran-4-yloxy)-benzo[*b*]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.** The final step amino tetrazole coupling was carried out under the following conditions: Intermediate 6 (0.183 g, 0.568 mmol) was dissolved in anhydrous CH_2Cl_2 (2.8 mL) in an argon-purged flask. A catalytic drop of DMF followed by oxalyl chloride (0.054 mL, 0.625 mmol) were added via syringe. The reaction was stirred at room temperature for five minutes. Acetonitrile (2.8 mL) and then 5-aminotetrazole (0.097 g, 1.14 mmol) and triethylamine (0.159 mL, 1.14 mmol) were added. The reaction was stirred at reflux for 20 minutes and then was allowed to cool to room temperature. The reaction was diluted with H_2O and acidified with 1N HCl until a solid precipitated. The solid was filtered and rinsed with H_2O. The filter cake slurried in a minimum MeOH and filtered again and dried *en vacuo* to give the title product (0.192 g, 0.494 mmol, 87 % yield). MS: M+1=390.1 (APCI). Microanalysis ($C_{17}H_{19}N_5O_4S$) calculated: C-52.43, H-4.92, N-17.98; experimental C-52.53, H-4.72, N-17.92.

Examples 2-18 were synthesized in a manner analogous to Example 1 by substituting an appropriately substituted alcohol for tetrahydro-4H-pyran-4-ol.

Example 2. **5-Methoxy-6-methyl-3-(3-methyl-cyclohexyloxy)-benzo[*b*]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 3. **5-Methoxy-6-methyl-3-(3,3,5,5-tetramethyl-cyclohexyloxy)-benzo[*b*]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 4. **5-Methoxy-6-methyl-3-(3,3,5-trimethyl-cyclohexyloxy)-benzo[*b*]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 5. **3-(3,3-Dimethyl-cyclohexyloxy)-5-methoxy-6-methyl-benzo[*b*]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 6. **3-Cyclohexyloxy-5-methoxy-6-methyl-benzo[*b*]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 7. **5-Methoxy-6-methyl-3-(3-methyl-cyclohexyloxy)-benzo[*b*]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 8. **3-Cycloheptyloxy-5-methoxy-6-methyl-benzo[*b*]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 9. **3-(1-Benzyl-piperidin-4-yloxy)-5-methoxy-6-methyl-benzo[*b*]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 10. **5-Methoxy-6-methyl-3-(piperidin-3-yloxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl amide.**

Example 11. **3-(1-Cyclohexyl-piperdin-4-yloxy)-5-methoxy-6-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl-amide).**

Example 12. **5-Methoxy-6-methyl –3-(piperidiny-4yloxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)amide.**

Example 13. **3-(1-Acetyl-piperidin-3-yloxy)-5-methyoxy-6-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 14. **3-[5-methoxy-6-methyl-2-(2Htetrazol-5-ylcarbamoyl)-benzo[b]thiophen-3-yloxy-piperdine-1-carboxylic acid tert-butyl ester.**

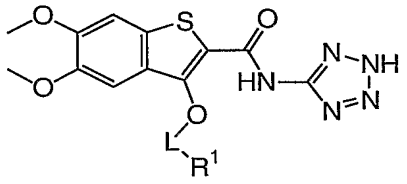
Example 15. **3-(3-Cyclohexyl-propoxy)-5-Methoxy-6-methyl-benzo[b}thiophene-2-carboxylic acid (2H-tetrazol-5-yl) amide.**

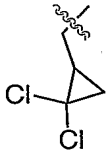
Example 16. **3-(1-Acetyl-piperidin-4-yloxy)-5-methoxy-6-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

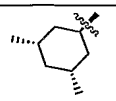
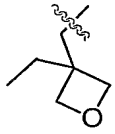
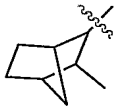
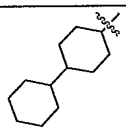
Example 17. **4-[5-Methoxy-6-methyl-2-(2H-tetrazol-5-ylcarbamoyl)-benzo[b]thiophene-3-yloxy]-piperidine-1-carboxylic acid tert-butyl ester.**

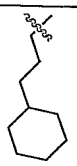
Example 18. **5-Methoxy-6-methyl-3-(1-methyl-cyclopropylmethoxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Examples 19-36



Ex.	-L-R^1	MS (M+1)
19		390.2
20		444.1
21		418.2
22		404.1
23		460.1

Ex.	-L-R^1	MS (M+1)
24		432.1
25		405.4 (M-1)
26		417.5 (M-1)
27		391.4 (M-1)
28		419.5 (M-1)
29		443.5 (M-1)
30		485.6 (M-1)
31		403.5 (M-1)
32		415.5 (M-1)
33		431.5 (M-1)
34		431.5 (M-1)

Ex.	-L-R^1	MS (M+1)
35		376.2
36		446.2

Intermediate 7. **3-(2-Cyclopropyl-ethyl)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid methyl ester.** To a 0°C solution of 3-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid methyl ester (1.53 g, 5.70 mmol) (prepared as described in U.S. Patent No. 3,954,748) in THF (25mL) under N_2 was added triphenylphosphine (1.53 g, 5.83 mmol) and diethylazodicarboxylate (DEAD) (0.90 mL, 5.72 mmol). The solution was stirred at 0°C for 40 minutes and then 2-cyclopropyl-ethanol (0.51 g, 5.92 mmol) was added. The reaction was stirred at 0°C for ten minutes and then at room temperature for 18 hours. The reaction mixture was concentrated *en vacuo*. The resulting oil was slurried in a minimum of diethyl ether at room temperature for one hour to give a white solid precipitate. The mix was filtered. The mother liquors were concentrated and purified by silica gel flash chromatography (ethyl acetate-hexanes (10%-15%-20%)) to give the title product (1.17 g, 3.48 mmol, 61%) as a pale purple solid.

Intermediate 8. **3-(2-Cyclopropyl-ethyl)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid.** To a solution of Intermediate 7 (1.16 g, 3.45 mmol) in THF (5 ml) was added 1M NaOH (5 mL). The reaction mixture was heated to reflux and stirred overnight. After cooling to room temperature, the solution was acidified with 1N HCl then diluted with excess water and extracted three times with ethyl acetate. The ethyl acetate extracts were dried over $MgSO_4$, filtered, and concentrated *en vacuo* to the title compound (1.00 g, 3.11 mmol, 90%) as a white solid.

Example 19. **3-(2-Cyclopropyl-ethoxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.** To a stirring solution of intermediate 8 (0.325 g, 1.01 mmol) in THF (5 mL) was added first DMF (1 drop) and then oxalyl chloride (0.18 mL, 2.06 mmol). The reaction was stirred at room temperature for 2.3 hours and then was concentrated *en vacuo* to give a yellow solid. The solid was redissolved in THF (5 mL) to which was then added 5-aminotetrazole (0.107 g, 1.25 mmol) and triethylamine (0.351 mL, 2.53 mmol). The reaction was stirred at room temperature for 20 hours and then at 50°C for 23 hours. The mixture was diluted with water and the resulting solid was filtered and rinsed with methanol to give the title compound (0.174 g, 0.447 mmol, 44%) as a solid.

The title compounds of Examples 20-36 were synthesized in a manner analogous to Example 19 by substituting an appropriately substituted alcohol for 2-cyclopropyl-ethanol.

Example 20. **3-(2,2-Dichloro-cyclopropylmethoxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 21. **3-Cyclohexylmethoxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 22. **3-Cyclohexyloxy-5,6-dimethoxy -benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 23. **3-(4-tert-Butyl-cyclohexyloxy)-5,6-dimethoxy - benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 24. **3-(3,5-dimethyl-cyclohexyloxy)-5,6-dimethoxy - benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.**

Example 25. **5,6-Dimethoxy-3-(3-methyl-oxetan-3-ylmethylmethoxy)-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 26. **5,6-Dimethoxy-3-(2-methyl-cyclohexyloxy)-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 27. **5,6-Dimethoxy-3-(tetrahydro-furan-3-yloxy)-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 28. **3-(3-Ethyl-oxetan-3-ylmethoxy)-5,6dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 29. **5,6 Dimethoxy-3-(3-methyl-bicyclo[2.2.1]hept-2-ylmethoxy)-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 30. **3-(Bicyclohexyl-4-yloxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 31. **5,6-Dimethoxy-3-(3-methyl-cyclopentyloxy)-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 32. **3-(Cyclohex-3-enylmethoxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

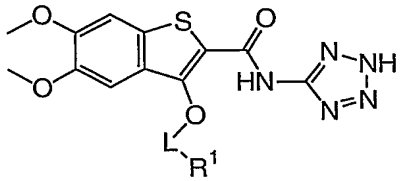
Example 33. **3-Cyclooctyloxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

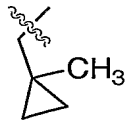
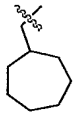
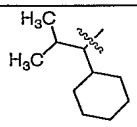
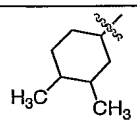
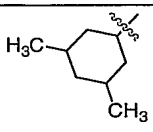
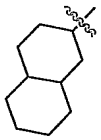
Example 34. **3-(3,5-Dimethyl-cyclohexloxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

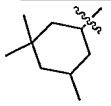
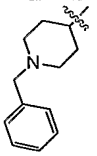
Example 35. **3-Cyclopropylmethoxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 36. **3-(3-Cyclohexyl-propoxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Examples 37-50



Ex.	-L-R^1	MS (M+1)
37		390
38		390
39		418
40		376
41		406
42		431
43		403
44		446
45		432
46		432
47		458

Ex.	-L-R^1	MS (M+1)
48		446
49		495
50		390

Intermediate 9. **5,6-Dimethoxy-3-(2-methoxy-ethoxymethoxy)-benzo[b]thiophene-2-carboxylic acid methyl ester.** A solution of 3-hydroxy-5,6-dimethoxy-3-benzo[b]thiophene-2-carboxylic acid methyl ester (10 g, 37.3 mmol, Conner et al. (1992) *J. Med. Chem.* 35: 958-965) in THF (300mL), was treated portion wise with NaH (60% oil dispersion, 1.56g, 39.1mmol) and allowed to stir for one half hour. MEM-Cl (4.6 mL, 41.0mmol) was added and the mixture was allowed to stir for 18 hours. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate. The solution was washed with NaOH (1N), brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Recrystallization from hot ethyl acetate afforded the title product (8.8 g, 66%). ^{1}H-NMR (400 MHz, D_6 DMSO) δ, 7.50 (s, 1H), 7.22(s,1H), 5.35(s, 2 H), 3.84 (m, 2H), 3.81 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.43 (m, 2H), 3.17 (s, 3H).

Intermediate 10. **5,6-Dimethoxy-3-(2-methoxy-ethoxymethoxy)-benzo[b]thiophene-2-carboxylic acid.** A solution of Intermediate 9 (8.8 g 24.7mmol), THF (100 mL), water (90mL) , and NaOH (1N, 61mL, 60.1 mmol) was heated to 50 °C for 3 hours. The THF was removed under reduced pressure and HCl was added to a final pH=3.5. The compound was recovered by filtration to afford the title product (6.5 g, 76%). ^{1}H-NMR (400 MHz, D_6 DMSO) δ, 7.47 (s, 1H), 7.20 (s, 1H), 5.35 (s, 2H), 3.84 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.42 (m, 2H), 3.16 (s, 3H).

Intermediate 11. **3-Hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid-Polymer supported.** A solution Intermediate of 10 (6.5g, 19mmol), di-isopropyl carbodiimide (3.12 mL, 19.9 mmol), and dichloromethane (70 mL) was allowed to stir for one half hour. The solution was added to a shaker flask containing Marshall resin (5.4g, 1.4mmol/g; Marshall and Liener (1970) *J. Org. Chem.* 35: 867-868), DMAP (4-dimethylaminopyridine) (0.92g, 7.0mmol), and dichloromethane. The reaction was allowed to gently shake for 18 hours. The resin was removed by filtration, washed with dichloromethane, dimethylformamide (DMF), and hexane, and dried under reduced pressure to afford 8.8 g. The resin was treated with dichloromethane (90mL) and triflouroacetic acid (30mL) for a period of 3 hours. The resin was removed by filtration and washed with dichloromethane, DMF, methanol, dichloromethane, and hexane. The resin was dried to a constant weight of 7.1 g (100%) (Theoretical 7.1g) to afford the title product.

Examples 37 to 50 were synthesized in the following manner. Intermediate 11 was placed into Irori Maxi Cans (approximately 250 mg resin per can), placed in a 20 mL glass jar and treated with dichloromethane (4 mL). The cans were shaken for 10 minutes, drained of solvent and treated again with dichloromethane (3 ml). A solution of the desired alcohol R^1-L-OH (4.2 ml, 0.71 M) in dichloromethane, was treated with a solution triphenylphosphine / diethylazodicarboxylate (DEAD) (5.0 mL, 0.599 M triphenylphosphine /DEAD) and allowed to stir for 20 minutes. To the desired jar was added the respective R^1-L-OH / triphenylphosphine / DEAD solution (5 mL). The cans were shaken for 4 hours in their capped jars and the reagents removed by suction. The cans were washed twice with dichloromethane (4 ml), twice with DMF (4 ml), twice with dichloromethane (4 ml), and then twice with hexane (4 mL). The cans were dried in a vacuum oven under reduced pressure for 0.5 hours. The above described reactions and subsequent washes were carried out an additional two times for each of the respective resin bound substrate and R^1-L-OH. To each of the reactions was added THF (1.5 ml), acetonitrile (3 ml), 5-amino tetrazole (0.089 g, 1.05 mmol), and triethylamine (TEA) (0.097 mL, 0.7 mmol). The jars were capped and heated to 70°C for 20 hours. The solutions were transferred to individual containers and

the resin washed once with THF (2 ml), twice with DMF (1 ml), and then once again with THF (1 ml). The washes were combined with the mother liquor and the solvent removed under reduced pressure. The title compounds could be purified by reverse phase chromatography or recrystallized from methanol /water/ triethylamine/ HCl.

Example 37. **5,6-Dimethoxy-3-(1-methyl-cyclopropylmethoxy)-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 38. **3-Cyclobutylmethoxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 39. **3-Cycloheptyloxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 40. **3-Cyclobutoxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 41. **5,6-Dimethoxy-3-(tetrahydro-pyran-4-yloxy)-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 42. **3-Cycloheptylmethoxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 43. **3-Cyclopentylmethoxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 44. **3-(1-Cyclohexyl-propoxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 45. **3-(3,4-Dimethyl-cyclohexyloxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 46. **3-(3,5-Dimethyl-cyclohexyloxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

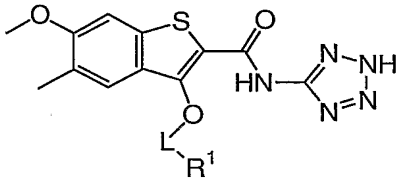
Example 47. **3-(Decahydro-naphthalen-2-yloxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

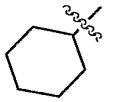
Example 48. **5,6-Dimethoxy-3-(3,3,5-trimethyl-cyclohexyloxy)-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 49. **3-(1-Benzyl-piperidin-4-yloxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 50. **3-Cyclopentyloxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.**

Example 51



Ex.	-L-R^1	MS (M+1)
51		388.1

Intermediate 12. **3-(3-methyl-4-methoxy-phenyl)-acrylic acid.** 3-methyl-4-methyloxybenzaldehyde (50.0 g, 333 mmol) was refluxed with malonic acid (52.0 g, 500 mmol) in a mixture of piperidine (15 mL) and pyridine (400 mL) for 11 hours. The mix was concentrated to one half volume. H_2O (~20 mL) and 1N HCl (~6 mL) were added to give a solid precipitate. The solid was filtered and rinsed with 1N HCl and then H2O and then was dried en vacuo to give the title product in quantitative yield.

Example 51. **3-Cyclohexyloxy-6-methoxy-5-methyl-benzo[*b*]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide** was synthesized from Intermediate 12 in a manner analogous to Example 1 by substituting cyclohexanol for tetrahydro-4H-pyran-4-ol.

BIOLOGICAL EXAMPLE 1

PI3Kγ Protein Expression and Purification Protocol

Spodtera frugiperda cells, grown in ESF921 media, were coinfected with baculovirus expressing a glu-tagged p101 and baculovirus expressing an HA-tagged p110γ, at a 3:1 ratio of p101 baculovirus to p110γ baculovirus. Sf9 cells were grown to 1×10^7 total cells/mL in 10L bioreactors and harvested 48-72 hours post infection. Samples of infected cells were then tested for expression of p101/p110γ PI3 kinase by immunoprecipitation and Western Blot analysis methods (see below).

To purify PI3Kγ, 4 volumes of room temperature hypotonic lysis buffer (1 mM $MgCl_2$, 1 mM DTT, 5 mM EGTA, 1 mM Pefabloc, 0.5 μM aprotinin, 5 μM leupeptin, 2 μM pepstatin, 5 μM E64, pH 8) per gram of cell paste, was poured onto frozen cell pellets with stirring, then lysed in a nitrogen "bomb" at 400 psi (599HC T316, Parr Instrument Co, Moline, IL). NaCl was added to 150 mM, and sodium cholate was added to 1% and mixed for another 45 minutes. The lysates were clarified by centrifugation for 25 minutes at 14,000 rpm. The lysates were then loaded over anti-glu-linked Protein-G Sepaharose beads (Covance Research Products, Richmond, CA) using 20 mL resin/50 g cell paste. The column was washed with 15 volumes of wash buffer (1 mM DTT, 0.2 mM EGTA, 1 mM Pefabloc, 0.5 μM aprotinin, 5 μM leupeptin, 2 μM pepstatin, 5 μM E64, 150 mM NaCl, 1% sodium cholate, pH 8). PI3Kγ was eluted with 6 column volumes of wash buffer that contain 100 μg/mL of a peptide that competes for binding of the glu tag. The column fractions with the eluted protein (determined by taking OD_{280} readings) were collected and dialyzed in 0.2 mM EGTA, 1 mM DTT, 1 mM Pefabloc, 5 μM leupeptin, 0.5% sodium cholate, 150 mM NaCl, and 50% glycerol, pH 8. The fractions were stored at -80°C until further use.

BIOLOGICAL EXAMPLE 2

G Protein Subunits Expression

Spodtera frugiperda cells were coinfected with baculovirus expressing a glu-tagged G protein β_1 and baculovirus expressing a G protein β_2, at a 1:1 ratio

of glu-tagged G protein β_1 baculovirus to G protein β_2 baculovirus. Sf9 cells are grown in 10 L bioreactors and harvested 48-72 hours post infection. Samples of infected cells were tested for G protein β_1/β_2 expression by Western Blot analysis, as described below. Cell lysates were homogenized and loaded onto a column of glu-tagged beads as in Biological Example 1 and competed off the column with a glu peptide and processed as described in Biological Example 1.

BIOLOGICAL EXAMPLE 3

Western Blot Analysis

Protein samples were run on an 8% Tris-Glycine gel and transferred to a 45 μM nitrocellulose membrane. The blots were then blocked with 5% bovine serum albumin (BSA) and 5% ovalbumin in TBST (50 mM Tris, 200 mM NaCl, 0.1% Tween 20, ph 7.4) for 1 hour at room temperature, and incubated overnight at 4°C with primary antibody diluted 1:1000 in TBST with 0.5% BSA. The primary antibodies for the p110γ, p110α, p110β, p85α, G protein β_1, and G protein γ_2 subunits were purchased from Santa Cruz Biotechnology, Inc., Santa Cruz, CA. The p101 subunit antibodies were developed at Research Genetics, Inc., Huntsville, AL based on a p101 peptide antigen.

After incubation with the primary antibody, the blots were washed in TBST and incubated for 2 hours at room temperaure with goat-anti-rabbit HRP conjugate (Bio-Rad Laboratories, Inc., Hercules, CA, product Number 170-6515), diluted 1:10,000 in TBST with 0.5% BSA. The antibodies were detected with ECL™ detection reagents (Amersham Biosciences Corp., Piscataway, New Jersey) and quantified on a Kodak ISO400F scanner.

BIOLOGICAL EXAMPLE 4

Immunoprecipitation

100 μL of cell paste from Biological Example 1 or 2 was thawed and lysed on ice with 400 μL of hypotonic lysis buffer (25 mM tris, 1 mM DTT, 1 mM EDTA, 1 mM Pefabloc, 5 μM leupeptin, 5 μM E-64 (Roche), 1% Nonidet P40, pH 7.5-8). The lysate was incubated for 2 hours at room temperature with glu-tagged beads (Covance Research Products, Cambridge, England, product Number

AFC-115P). The beads were washed 3 times in wash buffer (20 mM Tris, pH 7.8-8, 150 mM $NaCl_2$, 0.5% NP40) and the protein eluted off the beads by heating in 2 times sample buffer (Invitrogen Corporation, Carlsbad, CA, product Number LC1676).

BIOLOGICAL EXAMPLE 5

PI3Kγ In Vitro Kinase Assay

The inhibitory properties of the compounds in Table 1 were assayed in an in vitro PI3K assay. In a 96-well polypropylene plate, each well was spotted with 2 μL of 50 times the desired final concentration of compound in DMSO. Purified recombinant p101/p110γ protein (0.03 μg; ~2.7 nM) and G protein β_1/γ_2 subunits (0.09 μg; ~57.7 nM) for each reaction was combined in the assay buffer (30 mM HEPES, 100 mM NaCl, 1 mM EGTA, and 1 mM DTT). ATP and [γ-^{32}P-ATP] (0.09 μCi) were added to this mixture so that the final ATP concentration in the reaction was 20 μM. Lipid micelles were formed by sonicating phosphatidylinositol-4,5-diphosphate (PIP_2), phosphatidylethanolamine (PE), and Na-cholate in the assay buffer for 10 minutes, adding $MgCl_2$ and incubating on ice for 20 minutes, for final concentrations of 25 μM PIP_2, 300 μM PE, 0.02% Na-cholate, and 10 mM $MgCl_2$ in the reaction. The reactions were started by adding equal volumes lipid and enzyme mixture in a total volume of 50 μL, allowed to run for 20 minutes at room temperature, and stopped with 100 μL 75 mM H_3PO_4. The lipid product was transferred to a glass fiber filter plate and washed with 75 mM H_3PO_4 several times. The presence of radioactive lipid product (PIP_3) was measured by adding Wallac Optiphase mix to each well and counting in a Wallac 1450 Trilux plate reader (PerkinElmer Life Sciences Inc., Boston, MA 02118). The IC_{50} for each compound tested is reported in μM in Table 1:

Example	IC_{50} (μM)
1	0.024
2	0.024
3	0.165
4	0.009
5	0.008
6	0.007
7	0.003
8	0.005
9	0.250
10	1.290
11	0.965
12	0.715
13	0.072
14	0.053
15	0.028
16	0.025
17	0.024
18	0.020
19	0.371
20	0.453
21	0.195
22	0.034
23	0.056
24	0.103
25	0.445
26	0.101
27	0.575
28	0.245
29	0.014
30	0.110

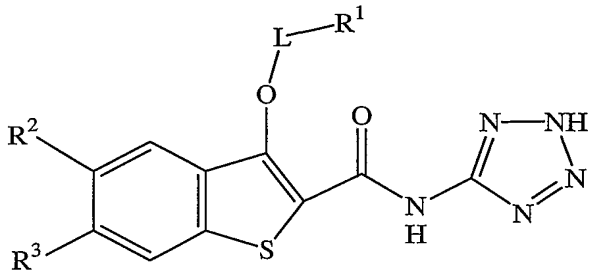
Example	IC_{50} (μM)
31	0.063
32	0.101
33	0.048
34	0.032
35	0.350
36	0.023
37	0.051
38	0.072
39	0.037
40	0.092
41	0.083
42	0.036
43	0.101
44	0.160
45	0.052
46	0.030
47	0.112
48	0.170
49	2.550
50	0.120
51	0.020

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

CLAIMS

What is claimed is:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof;

wherein R^2 and R^3 are selected from the group consisting of:

(i) R^2 is methoxy and R^3 is methyl or methoxy; and

(ii) R^2 is methyl and R^3 is methoxy;

wherein L is absent, or a C_1-C_4-alkylene;

wherein R^1 is C_3-C_8 cycloalkyl, a C_5-C_8 cycloalkenyl, a 4- to 6-membered heterocycloalkyl, a tetrahydropyranyl, a piperidinyl, a oxetanyl, a tetrahydrofuranyl, a bicyclo[2.2.1]heptyl, or a decahydro-naphthalenyl,

wherein R^1 can be optionally substituted with 4 methyls, a C_1-C_2 alkylene-6-membered heterocycloalkyl, or from 1 to 3 substitutents independently selected from the group consisting of:

C_1-C_4 alkyl, methyl, tert-butyl, $C(O)CH_3$, $C(O)O$-C_1-C_4alkyl, CH_2-phenyl, a C_5-C_6 cycloalkyl, Cl, Br, F, $-CF_3$, -OH, $-OCF_3$, and O-C_1-C_6alkyl.

2. The compound of claim 1, wherein R^2 is methoxy, and R^3 is methyl.

3. The compound of claim 2, wherein R^1 is an optionally substituted group selected from the group consisting of:
tetrahydropyranyl, C_6-cycloalkyl, C_7-cycloalkyl, and piperidinyl.

4. The compound of claim 2, wherein said compound is selected from the group consisting of:

5-Methoxy-6-methyl-3-(tetrahydro-pyran-4-yloxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

5-Methoxy-6-methyl-3-(3,3,5,5-tetramethyl-cyclohexyloxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

5-Methoxy-6-methyl-3-(3,3,5-trimethyl-cyclohexyloxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

3-(3,3-Dimethyl-cyclohexyloxy)-5-methoxy-6-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

3-Cyclohexyloxy-5-methoxy-6-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

5-Methoxy-6-methyl-3-(3-methyl-cyclohexyloxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

3-Cycloheptyloxy-5-methoxy-6-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

3-[5-methoxy-6-methyl-2-(2Htetrazol-5-ylcarbamoyl)-benzo[b]thiophen-3-yloxy-piperdine-1-carboxylic acid tert-butyl ester;

3-(3-Cyclohexyl-propoxy)-5-Methoxy-6-methyl-benzo[b}thiophene-2-carboxylic acid (2H-tetrazol-5-yl) amide;

3-(1-Acetyl-piperidin-4-yloxy)-5-methoxy-6-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

4-[5-Methoxy-6-methyl-2-(2H-tetrazol-5-ylcarbamoyl)-benzo[b]thiophene-3-yloxy]-piperidine-1-carboxylic acid tert-butyl ester; and

5-Methoxy-6-methyl-3-(1-methyl-cyclopropylmethoxy)-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.

5. The compound of claim 1, wherein R^2 is methoxy and R^3 is methoxy.

6. The compound of claim 5, wherein R^1 is an optionally substituted group selected from the group consisting of:

C_3-cycloalkyl, C_6-cycloalkyl, C_6-cycloalkenyl, and bicyclo[2.2.1]heptyl.

7. The compound of claim 5, wherein said compound is selected from the group consisting of:

3-(2,2-Dichloro-cyclopropylmethoxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

3-Cyclohexyloxy-5,6-dimethoxy -benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

3-(4-tert-Butyl-cyclohexyloxy)-5,6-dimethoxy -benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide;

5,6 Dimethoxy-3-(3-methyl-bicyclo[2.2.1]hept-2-ylmethoxy)-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide;

3-(Cyclohex-3-enylmethoxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide;

3-(3,5-Dimethyl-cyclohexloxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide; and

3-(3-Cyclohexyl-propoxy)-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (1H-tetrazol-5-yl)-amide.

8. The compound of claim 1, wherein R^2 is methyl and R^3 is methoxy.

9. The compound of claim 8, wherein R^1 is an optionally substituted C_6-cycloalkyl.

10. The compound of claim 8, wherein said compound is 3-Cyclohexyloxy-6-methoxy-5-methyl-benzo[b]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)-amide.

11. A method of treating a subject suffering from a PI3K-mediated disorder or condition comprising:

administering, to a subject suffering from a PI3K-mediated condition or disorder, a pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

12. The method of claim 11, wherein said PI3K-mediated condition or disorder is selected from the group consisting of:

rheumatoid arthritis, osteoarthritis, psoriatic arthritis, psoriasis, inflammatory diseases, and autoimmune diseases.

13. The method of claim 11, wherein said PI3K-mediated condition or disorder is selected from the group consisting of:

cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, coronary artery disease, cancer, breast cancer, gliobastoma, endometrial carcinoma, heptocellular carcinoma, colon cancer, lung cancer, melanoma, renal cell carcinoma, thyroid carcinoma, small cell lung cancer, squamous cell lung carcinoma, glioma, breast cancer, prostate cancer, ovarian cancer, cervical cancer, leukemia, cell lymphoma, lymphoproliferative disorders, type II diabetes, respiratory diseases, bronchitis, asthma, and chronic obstructive pulmonary disease.

14. The method of claim 11, wherein said compound is a compound of any one of claims 1-10.

15. A pharmaceutical composition comprising:

a therapeutically effective amount of a compound of any one of claims 1-10 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
/IB2004/001783

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D409/12 C07D409/14 A61K31/41 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 187 487 A (WARNER LAMBERT CO) 16 July 1986 (1986-07-16) claim 1	1-15
A	EP 0 299 457 A (WARNER LAMBERT CO) 18 January 1989 (1989-01-18) claim 1	1-15
A	US 5 426 113 A (LOW JOSEPH E) 20 June 1995 (1995-06-20) claim 1	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 2004	23/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Wolf, C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/001783

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
/IB2004/001783

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